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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,146	HAUER ET AL.	
	Examiner	Art Unit	
	YONG D. PAK	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-49* is/are pending in the application.

4a) Of the above claim(s) *38-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP00/07253.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 3, 2010, canceling claims 1-10, 12-14 and 16-24 and adding claims 27-49, has been entered.

Claims 27-49 are pending. Claims 38-49 are withdrawn. Claims 27-37 are under consideration.

Election/Restrictions

Newly submitted claims 38-49 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 38-40 belong to Group I, drawn to a P450 monooxygenase. Claims 41-45 belong to Group II, drawn to polynucleotides encoding a P450 monooxygenase. Claims 46-48 belong to Group IV, drawn to a method for the microbiological oxidation of optionally substituted mono- or polynuclear aromatics, straight-chain or branched alkanes or alkenes of

cycloalkanes or cycloalkenes. Claim 49 belongs to Group V, drawn to a bioreactor comprising a P450 monooxygenase.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 38-49 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Arguments

Applicant's amendment and arguments filed on February 3, 2010, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 27 and 36 are objected to because of the following informalities: The claim recites the phrase "Bacillus megaterium" which should be italicized. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In view of the cancellation of claims 17-18, the rejection of claims 17-18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been **withdrawn**.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim Rejections - 35 USC § 112- 1st paragraph

In view of the cancellation of claims 9-10, 12 and 17-18, the rejection of claims 9-10, 12 and 17-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, has been **withdrawn**.

In view of the cancellation of claims 9-10, 12 and 17-18, the rejection of claims 9-10, 12 and 17-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, has been **withdrawn**.

Claims 33-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 33-35 are drawn to a method for the microbiological production of indigo and/or indixubin by incubating an indole-containing reaction medium with an indole-oxidizing cytochrome P450. It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow.". In this case, the examiner has broadly interpreted the claims to encompass a method of producing indigo and/or indixubin from indole by using a genus of indole-oxidizing cytochrome P450 isolated from any or all sources, including any or all variants thereof.

In *University of Calfornia v. Eli Lilly & Co.,* 43 USPQZd 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a

combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The recitation of "indole-oxidizing cytochrome P450 monooxygenase" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "indole-oxidizing cytochrome P450 monooxygenase" proteins used in the claimed method, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the

protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Therefore, in the instant case, the claim is drawn to method of producing indigo and/or indixubin from indole by using a genus of indole-oxidizing cytochrome P450 having unknown structure. The specification only describes one representative species, a method for oxidizing indoles with a modified cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the modified P450 monooxygenase consists of mutations at residue Phe87Val, Phe87Val and Leu 188Gin, or Phe87Val, Leu188GIn and/or Ala74Gly. While MPEP 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In view of the widely variant species encompassed by the genus, this one example is not enough and does not constitute a representative number of species to describe a method of producing indigo and/or indixubin from indole using a whole genus of any or all variants, recombinant and mutants of any or all polypeptides having indole-oxidizing cytochrome P450 monooxygenase activity isolated from any or all source, including any or all variants, recombinants and mutants thereof, and there is no evidence on the record of the relationship between the structure of the specific mutants of SEQ ID NO:2 and the structure of any or all recombinant, variant and mutant of any or all polypeptides having indole-oxidizing cytochrome P450 monooxygenase activity. Therefore, the specification fails to describe a representative species of a method of using the genus

comprising any or all polypeptides having indole-oxidizing cytochrome P450 monooxygenase activity, including any or all variants, recombinants and mutants thereof.

Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for oxidizing indoles with a modified cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the modified P450 monooxygenase consists of mutations at residue Phe87Val, Phe87Val and Leu 188Gin, or Phe87Val, Leu188GIn and/or Ala74Gly, does not reasonably provide enablement for a method for oxidizing indoles with a modified cytochrome P450 monooxygenase having unknown structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 33-35 are drawn to a method for the microbiological production of indigo and/or indixubin by incubating an indole-containing reaction medium with an indole-oxidizing cytochrome P450.

The breadth of the claims.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow.". In this case, the examiner has broadly interpreted the claims to encompass a method of producing indigo and/or indixubin from indole by using any indole-oxidizing cytochrome P450 monooxygenase isolated from any or all sources, including any or all variants thereof, having unknown structure. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of serine proteases isolated from any or all source, including any or all mutants, recombinants and variants thereof. In the instant case, the specification enables only a method for oxidizing indoles with a

modified cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the modified P450 monooxygenase consists of mutations at residue Phe87Val, Phe87Val and Leu 188Gin, or Phe87Val, Leu188GIn and/or Ala74Gly.

The state of prior art, the relative skill of those in the art, and predictability or unpredictability of the art.

Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within a cytochrome P450 monooxygenase can be modified and which ones are conserved such that one of skill in the art can make the recited polypeptides having indole-oxidizing cytochrome P450 monooxygenase activity, (2) which segments of SEQ ID NO:2 are essential for activity, and (3) the general tolerance of cytochrome P450 monooxygenase to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden

et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions.

The amount of direction or guidance presented and the existence of working examples.

The specification discloses a method for oxidizing indoles with a modified cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the modified P450 monooxygenase consists of mutations at residue Phe87Val, Phe87Val and Leu 188Gin, or Phe87Val, Leu188GIn and/or Ala74Gly. However, the speciation fails to provide any information as to (1) specific substrates associated with any indole-oxidizing cytochrome P450 monooxygenase isolated from any source, including variants, mutants and recombinants thereof, (2) structural elements required in a polypeptide having indole-oxidizing cytochrome P450 monooxygenase activity, or (3) which are the structural elements in a indole-oxidizing cytochrome P450 monooxygenase that are essential to display indole-oxidizing cytochrome P450 monooxygenase activity. No correlation between structure and function of having indole-oxidizing cytochrome P450 monooxygenase activity has been presented. There is no information or guidance as to which amino acid residues in any cytochrome P450 monooxygenase can be modified

and which ones are to be conserved to create a polypeptide displaying indole-oxidizing cytochrome P450 monooxygenase activity.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.

While enzyme isolation techniques, recombinant and mutagenesis techniques were known in the art at the time of the invention, e.g. hybridization or mutagenesis, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, it is not routine in the art to create variants of polynucleotides encoding polypeptides having the activity recited without any knowledge as to the structural features which would correlate with that activity.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability of the prior art in regard to structural changes and their effect on function and the lack of knowledge about a correlation between structure and function, an undue experimentation would be necessary one having ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the

claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics recited in the claims are unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Since claims 9-10, 12 and 17 have been cancelled, the rejections of claims 9-10, 12, and 17 under 35 U.S.C. 102(b) and 102(e) as being anticipated by Wong et al. has been withdrawn.

Claims 27-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Graham-Lorence et al.

Claims 27-37 are drawn to a method of oxidizing N-or S-heterocyclic mono or polynuclear aromatic compounds or indole with a mutant of the cytochrome P450 monooxygenase of SEQ ID NO:2, wherein said mutant consists of the mutation F87V.

Graham-Lorence et al. discloses a mutant of the cytochrome P450 monooxygenase of SEQ ID NO:2, wherein said mutant consists of the mutation F87V, abstract). Even though Graham-Lorence et al. is silent as to the indole-oxidizing activity of said F87V mutant, Examiner takes the position that the indole-oxidizing activity is an inherent property of said mutant and the reference of Graham-Lorence et al. anticipates the calimed method since the mutant F87V carries out the claimed process (method of oxidizing indole to indigo) during normal operation. Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. *In re King,* 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986), see MPEP 2112.01. Further, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. See MPEP 2112.02. Therefore, the reference of Graham-Lorence et al. anticipates claims 27-37.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652